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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/623,006	08/24/2000	Patrick Tso	10738-17	5310

7590 08/04/2006

Dinsmore & Shohl
1900 Chemed Center
255 East Fifth Street
Cincinnati, OH 45202

EXAMINER	
MITRA, RITA	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 08/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 09/623,006	Applicant(s) TSO ET AL.	
	Examiner Rita Mitra	Art Unit 1653	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 10 July 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☒ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1,4-14,19 and 64-66*.
   Claim(s) withdrawn from consideration: *67*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

Continuation of 3.

New claim 67 has been added. No claim from the finally rejected claims has been cancelled. Claim 67 has scope issue by reciting "derivatives, analogs and homologs."

Continuation of 11.

In regard to the rejection of claims 1, 4-14, 19 and 64-66 under **35 U.S.C. 112, first paragraph, written description.** Applicants argue at pages 8-10 that in order to enable the claimed invention, the independent claims have all been amended to specifically recite, that the apolipoprotein A-IV peptide employed in the presently inventive methods comprises an amino acid sequence substantially corresponding to at least one of the sequences set forth as SEQ ID NOs: 1-13. However independent amended claims 1, 13 and 14 have raised a new issue. The new issue is introducing amino acid sequence of SEQ ID NOs: 1-13 in the amended claims 1, 13 and 14. This requires a new search of the amino acid sequences recited in the amended claims. Further the amended claims reciting "substantially corresponding" makes the claim unclear.

As for the claim 4 Applicants should note that the language "substantially corresponding" would be interpreted by a skilled artisan that by definition in the specification an amino acid sequence having approximately 70% homology to a specifically recited amino acid sequence. Thus the amino acids sequence having 70% homology is a fragment of the full length of that specific sequence. Therefore, the specification lacks adequate written description to demonstrate to a skilled artisan that applicant was in possession of the claimed invention

As it is stated at page 12 of the specification that the invention provides for a number of lipid oxidation inhibiting peptides of approximately 5-90 amino acids in length, which substantially correspond in sequence to amino acid sequence found in specific portions of apo AIV, which is insufficient description as no characteristics are provided nor any evidence to demonstrate retention of function with regard to inhibitory activity in lipid oxidation. Moreover based on claim language "substantially corresponding" the claimed apolipoprotein can have enormous number of variants because the term "substantially corresponding" is defined as an

amino acid sequence having approximately 70% homology to a specifically recited amino acid sequence. It should be noted here that (see Final Rejection also) the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitution can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding the active sites. Particular regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitution or no substitutions. However, the specification provides no description of the positions in the protein, which are tolerant to change (e.g. by amino acid substitutions or deletions, insertion or/and addition), and the nature and extent of changes that can be made in these positions. Therefore, the skilled artisan cannot envision the detailed chemical structure of the apolipoprotein variants and fragments, thus, claims reciting said variants and/or fragments lack adequate written description.

In regard to the rejection of claims 1, 4-14, 19 and 64-66 under **35 U.S.C. 112, first paragraph, enablement.** Applicants argue at page 11 that in order to enable the claimed invention, the independent claims have all been amended to specifically recite, that the apolipoprotein A-IV peptide employed in the presently inventive methods comprises an amino acid sequence substantially corresponding to at least one of the sequences set forth as SEQ ID NOs: 1-13. However independent amended claims 1, 13 and 14 have raised a new issue. The new issue is introducing amino acid sequence of SEQ ID NOs: 1-13 in the amended claims 1, 13 and 14. This requires a new search of the amino acid sequences recited in the amended claims. Further the amended claims reciting "substantially corresponding" makes the claim unclear.

In the instant case, the amount of experimentation is required to practice the claimed invention is undue as the claims encompass an unspecified amount of apolipoprotein A-IV peptides and variants/fragments. One of skill in the art would have to make and test each one to determine if it had the apo A-IV activity of the parent protein. The amount of guidance presented

is limited to the exact sequence. There is no disclosure or description of the use of other apo A-IV protein fragments. There are no working examples indicating the claimed methods in association with the variants. Moreover, the specification has not shown the treating conditions using these apo A-IV variants, nor indicated the expected outcome of treatment. Without more guidance from the specification it would require undue and excessive experimentation for a person having skill in the art to be able to make and use the claimed variants.

The scope of the claims includes method of lipid oxidation associated with a condition in a patient comprising administering an apolipoprotein A-IV compound, wherein the compound is a peptide sequence, and a variant or fragment of apolipoprotein A-IV, but the specification does not show the treatment using these variants. The nature of the variants makes it entirely unpredictable what might be considered a variant before the isolation of such a sequence has actually taken place Thus, the disclosure is not enabling for the reasons discussed below.

The breadth of the claims is broad and encompasses an unspecified number of variants regarding the apolipoprotein A-IV protein products as biological active fragments, which are not specifically described or demonstrated in the specification. The specification indicates at page 6, lines 3-6 that a number of novel lipid oxidation suppressant peptides, derived from apolipoprotein A-IV, have been made, that possess lipid oxidation inhibiting properties which when administered orally or intravenously, can be used to decrease atherosclerosis. However, these peptides are not adequately described or demonstrated in the specification.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed variants, the guidance/the teaching in the specification is limited, and the outcome is unpredictable using various apolipoprotein A-IV products, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effect of the treatment using a apolipoprotein A-IV variants.

The rejection is set forth in prior office action. In response Applicants traverse the rejection (see page 10-15). The reason for the traversal in particular is with respect to working examples. It should be noted that there are no working examples indicating the claimed methods in association with the variants. Moreover, the specification has not shown the treating conditions using these apo A-IV variants. The requirement of a specific guidance on treating conditions, does not necessarily require disclosures of clinical data as interpreted and stated by

the Applicants. The specification and the working examples do not provide any guidance with respect to use of the fragments or variants for the treatment. Since the specification fails to provide sufficient guidance on the treating conditions for various apo A-IV variants, it is necessary to have additional guidance on the identities of apo A-IV variants and to carry out further experimentation to assess the effect of an apo A-IV variant, which is used for the treatment.

The amendment to claims 1, 13 and 14 has not overcome the ground of rejection under 35 U.S.C. 112, first paragraph for fragments and variants of apolipoprotein A-IV. Therefore, claims 1-4, 14, 19, 64-66 stand rejected under **35 U.S.C. 112, first paragraph.**

Rita Mitra, Ph.D.
July 26, 2006

Jon Weber
Supervisory Patent Examiner